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The Reactions of the Formamidines: XI, The 2-Thio-4-Thiazolidones.

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THE previous papers in this field have shown that compounds containing methylene hydrogen, $=CH_2$, reacted with the aryl formamidines, RNHCH(NR), and gave aminomethylene derivatives of the type $>C=CHNHR$. Such activity was shown not only by open-chain compounds such as acetoacetic ester, malonic ester, etc., but also by ring derivatives such as the pyrazolones, thiazolidones and imidazolones. (1) For instance, diphenylformamidine and diphenylisothiohydantoin gave 2-phenyl-imino-3-phenyl-5-anilino-methylene-4-thiazolidone, $\underbrace{SC(NPh)NPhCOC}=CHNHPh$.

Corresponding results were obtained in the case of the mono and the unsubstituted thiazolidones. (2)

The isomeric thioimidazolones showed the same behavior so far as the methylene group was concerned, but the interesting observation was made that the mono substituted derivatives

$$\underbrace{HN\text{–}CSNRCOC}=CHNHR$$

were soluble in sodium hydroxide and formed thio ethers, just as were the corresponding aldehyde condensation products described by Wheeler and Johnson and their coworkers. (3)

In view of these facts, the 2-thio-4-thiazolidone,

$$\underbrace{\overset{1}{S}\text{–}\overset{2}{C}\overset{3}{S}NH(R)\overset{4}{C}O\overset{5}{C}H_2},$$

seemed worth investigating, since it contained the complex $-CO-CH_2S-$ of the ordinary thiazolidones, as well as the grouping $HN-CS-(=N-CSH-)$ of the thioimidazolones, and thus might

show the characteristic reactions of each type. The following experimental work has proved that this was the case. The 2-thio-4-thiazolidone not only gave aminomethylene and aldehyde condensation products at position 5, but also thio ethers at position 2. (4)

PREPARATION OF THE THIAZOLIDONES.

2-THIO-4-THIAZOLIDONE. The method first described by Nencki was followed. (5) One molar weight of chloroacetic acid with double its weight of water was added to three molar weights of ammonium thiocyanate. The mixture was heated on the water bath to 70° or until the reaction started. Later it was often necessary to cool the flask to prevent overheating. The yield, 18%, was not especially good. The purified product melted at 165°.

2-THIO-3-PHENYL(ARYL)-4-THIAZOLIDONE. $\underbrace{S\text{–}CSNRCOCH_2}$.

The general procedure for the syntheses of the 3-substituted thiazolidones was as follows:

Ammonium phenyldithiocarbonate, PhNHCSSNH. (6) A mixture of 108 gms. of carbon disulfide and 150 gms. of ammonium hydroxide (28%) was placed in a tall beaker cooled with ice. To this was added, with constant stirring, 112 gms. of aniline. Precipitation of the salt was usually complete in an hour. The product was then filtered and washed with alcohol and ether. The ammonium salt (one mol.) was made into a paste with water and treated with a concentrated solution of sodium chloracetate, stirring meanwhile, preferably with a turbine. The reaction mixture was allowed to stand for an hour and diluted with water. The solution was filtered, if necessary, and then acidified with an excess of acetic acid. (Sulphuric or hydrochloric acid can also be used.) Precipitation of the thiazolidone was complete after twenty-four hours. The usual yields were from 60 to 75%. It was purified by recrystallization from alcohol.

$$PhNHCSSNH_4 + Cl.CH_2COONa = NH_4Cl + PhNHCSSCH_2COONa.$$

$$PhNHCSSCH_2COONa + HCl = NaCl + PhNHCSSCH_2COOH = \underbrace{S\text{–}CSNPhCOCH_2} + H_2O.$$

2-Thio-3-tolylthiazolidone, $\underbrace{S\text{–}CSN(C_7H_7)COCH_2}$, prepared as above separated from alcohol in golden yellow crystals which melted at 115°. Since the melting point in literature (7) was given as 101°, the accuracy of the formula was confirmed by analyses.

Analysis: Calc. for $C_{10}H_9ONS_2$:N, 6.28. Found, 6.31.

CONDENSATION PRODUCTS OF THE THIAZOLIDONES WITH ALDEHYDES. (8)

These have been prepared in many cases, using sulphuric acid or sodium hydroxide as condensing agents. In this laboratory, piperidine has been found very satisfactory. Thus a solution of 2-thio-4-thiazolidone (18 gms.), benzaldehyde (14 gms.), in 200 cc. of absolute alcohol treated with a few drops of piperidine, gave an 83% yield of the 2-thio-5-benzal-4-thiazolidone. $\underline{S\text{–}CSNHCOC} = CHPh$. (m. p. 200:).

CONDENSATION OF THE THIAZOLIDONES WITH THE FORMAMIDINES.

2-Thio-5-anilino-methylene-4-thiazolidone. A molar mixture of diphenylformamidine and the thiazolidone was made into a thin paste with kerosene and then heated in an oil bath at 120° for one hour. Longer heating at higher temperatures should be avoided, since red, gummy decomposition products tend to be formed and the difficulties of purification are increased.

The reaction product was filtered, washed with a little cold alcohol and then recrystallized from alcohol. The yellow needles melted at 248°. The new compound, which was obtained in 46% yield, was soluble in hot alcohol and in aceton, difficultly soluble in benzene and gasoline and dissolved readily in sodium hydroxide solution.

$$\underline{S\text{–}CSNHCOCH_2} + C_6H_5NCHNHC_6H_5 = C_6H_5NH_2 + \underline{S\text{–}CSNHCOC} = CHNHC_6H_5.$$

Analysis: : Calc. for $C_{10}H_8ON_2S_2$:N, 11.87. Found, 11.64.

SUBSTITUTED THIAZOLIDONES.

2-THIO-3-PHENYL-5-ANILINO-METHYLENE-4-THIAZOLIDONE.

$$\underline{S\text{-}CS\text{-}N(C_6H_5)COC} = CHNHC_6H_5.$$

This was made by heating a mixture of diphenylformamidine and 3-phenyl-thiazolidone in kerosene solution at 120-30°. The yellow crystals from alcohol melted at 247° and were difficultly soluble in the usual organic solvents.

Calc. for $C_{16}H_{12}ON_2S_2$:N, 8.98. Found, 8.77.

CHEMICAL BEHAVIOR OF THE ABOVE ANILINO-METHYLENE DERIVATIVE.

(*a*) When heated for several hours on the water bath with alcoholic potassium hydroxide, the mole was completely disrupted, yielding as one product, aniline.

(*b*) When boiled with barium hydroxide the resulting solution contained barium sulphide and aniline and gave a positive test for the $HSCH_2CO$ radical, due doubtless to the formation of thioglycollic acid.

(*c*) It is much more stable toward acids. Very little decomposition was effected by heating for twelve hours with an alcoholic solution of hydrochloric acid.

(*d*) One gram of the substance in 30 cc. of alcohol was heated on the water bath for eight hours with four gms. of chloroacetic acid in 30 cc. of water. Under these conditions no desulfurization occurred.

(*e*) Aniline at 100° or 170° produced no change; but at 190° there was practically complete decomposition of the mole.

(*f*) The thiazolidone was boiled in alcohol solution for several hours with an excess of phenylhydrazine acetate. Hydrogen sulphide was evolved and from the solution was isolated a small amount of a reaction product, which separated from alcohol in dark red crystals with a melting point of 215°. It had a nitrogen content of 14.15% and may possibly be the 2-phenyl-hydrazone.

$$\begin{array}{l} \qquad\qquad C_6H_5N\text{–}COC = CHNHC_6H_5 \\ \qquad\qquad\qquad\quad | \qquad\quad | \\ C_6H_5HNN:C\text{——}S \end{array}$$

Analysis: Calc. for $C_{22}H_{18}ON_4S$; N:14.50.

Lack of time prevented further confirmation.

2–THIO–3–PHENYL–5–ALPHA–NAPHTHYL–AMINO–METHYLENE–4–THIAZOLIDONE.

$$\underbrace{S\text{–}CSN(C_6H_5)COC}\,= CHNHC_{10}H_7.$$

Equal mols of the dialphanaphthyformamidine and the phenylthiazolidone were heated in kerosene solution for four hours at 150°. The product was best purified from benzene and the yellow crystals melted at 279°. The yield was 36%.

Analysis: Calc. for $C_{20}H_{14}ON_2S_2$:N, 7.74. Found, 7.59.

2–THIO–3–PHENYL–5–p–METHOXY–ANILINO–METHYLENE–4–THIAZOLIDONE.

$$\underbrace{S\text{–}CSN(C_6H_5)COC}\,= CHNHC_6H_4OCH_3.$$

The di-p-anisylformamidine and the phenylthiazolidone were heated under the usual conditions. The new compound crystallized from alcohol in yellow needles which melted at 158-60°.

Analysis: Calc. for $C_{17}H_{14}O_2N_2S_2$:N, 8.19. Found, 8:00.

2-THIO-3-p-TOLYL-5-ANILINO-METHYLENE-4-THIAZOLIDONE.

$$\underbrace{SCSN(C_7H_7)COC}=CHNHC_6H_5.$$

In this case the condensation was carried out at 95°. The compound was difficultly soluble in hot alcohol, from which it crystallized in yellow needles with a melting point of 235°.

Analysis: Calc. for $C_{17}H_{14}ON_2S_2$:N, 8.59. Found, 8.54.

THIO ETHERS.

It was mentioned earlier in this article that the methylene substituted derivatives with the 3-position free could exist in an enol form, $\underbrace{S-C-(SH)NCOC}=CHR$, a statement proven by the ease with which they formed thio ethers.

THIO ETHERS FROM ALDEHYDE CONDENSATION PRODUCTS.

2-BENZYL-THIO-5-BENZAL-4-THIAZOLIDONE.

$$\underbrace{SC(SCH_2C_6H_5)N-COC}=CHC_6H_5.$$

The benzal-thiazolidone (10 gms.) was dissolved in 10% sodium hydroxide and to this was added benzyl chloride (6 gms.) in 150 cc. of water. The mixture was shaken thoroughly and allowed to stand for twenty-four hours. The crude precipitate, which was obtained in 96% yield, was purified from alcohol. The light-colored crystals melted at 123°.

Analysis: Calc. for $C_{17}H_{13}ONS_2$:N, 4.50. Found, 4.52.

2-BENZYL-THIO-5-CINNAMAL-4-THIAZOLIDONE.

$$\underbrace{S-C(SCH_2C_6H_5)NCOC}=CH:CHCHC_6H_5.$$

In this case an alcoholic solution of benzyl chloride was added to the cinnamal compound dissolved in sodium hydroxide. The ether was obtained in 88% yield, and after crystallization from alcohol, melted at 143°.

Analysis: Calc. for $C_{19}H_{15}ONS_2$:N, 4.15. Found, 4.11.

THIO ETHERS FROM THE FORMAMIDINE CONDENSATION PRODUCTS.

2-ETHYL-THIO-5-ANILINO-METHYLENE-4-THIAZOLIDONE.

$$\underbrace{SC(S-C_2H_5)NCOC}=CHNHC_6H_5.$$

The anilino compound was heated for an hour in alcohol solution with potassium hydroxide (1 mol.) and ethyl iodide. On cooling the greenish-yellow thio ether separated, and, when purified, melted at 175°.

Analysis: Calc. for $C_{12}H_{12}ON_2S_2$:N, 10.61. Found, 10.66.

2-BENZYL-THIO-5-ANILINO-METHYLENE-4-THIAZOLIDONE.

$$\underbrace{S\text{–}C(SCH_2C_6H_5)NCOC}=CHNHC_6H_5.$$

This was obtained in quantitative yield by treating an alkaline solution of the thiazolidone with benzyl chloride. It is best purified by crystallization from benzene. The light-yellow needles from this solvent melted at 221-3°.

Analysis: Calc. for $C_{17}H_{14}ON_2S_2$:N, 8.59. Found, 8.67.

SUMMARY.

(*a*) It has been shown that the 2-thio-thiazolidones react with the substituted formamidines, yielding 5-amino-methylene derivatives.

(*b*) The substituted aldehyde or aminomethylene thiazolidone which contains the grouping –CSNH or C–SHN =, give with ethyl or benzyl halide easily and smoothly the corresponding thio ethers.

(*c*) Several new compounds have been synthesized in illustrating the chemical behavior of the thio-thiazolidones. (9)

(1) Ber. Deut. Chem. Ges. 35, 2496 (1902).
Jour. Am. Chem. Soc. 31, 1148 (1909); 35, 959, 970 (1913); 38, 1510, 1841 (1916); 40, 562 (1918); 43, 613, 1200 (1921); 44, 2310 (1922).
(2) Jour. Am. Chem. Soc. 38, 1841 (1916); 43, 613 (1921).
(3) Jour. Am. Chem. Soc. 44, 2310 (1922).
Am. Chem. Jour. 45, 447 (1911).
(4) Bibliography of 2-Thio-Thiazolidones. Granacher-Helv. Chem. Acta III, 152.
(5) J. pr. Ch. (2) 16, 4 (1877).
(6) Kansas Univ. Sci. Bull., vol. 13, July, 1922. C. A. 17, 543 (1923).
(7) Monatsh. 26, 1192 (1905).
(8) Helv. Chem. Acta III, 158 (1920).
(9) The authors wish to thank the Research Committee of the University of Kansas for a grant which was of essential aid in this investigation.